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(54) Implantable biomedical sensor device, suitable in particular for measuring the concentration of glucose.

(57) Implantable biomedical sensor device for measuring in vivo the presence and/or concentration of physiological substances, such as the concentration of glucose, in the human or animal body. A miniaturized electronic responder (3) arranged in a housing (2) of biocompatible material is exchanging binary coded information with a transmitter/receiver (20) and is provided with electrical connections, passing through the wall of the housing, which constitute an active electrode (10), a counter-electrode (8) and preferably, also a reference electrode (9) outside the housing. The active electrode (10) comprises a membrane (13) with hollow fibres extending transversely to the surface of the membrane and whose internal walls are coated with a conductive polymer containing a redox enzyme. One end of the hollow fibres is in electrical contact with a processing device (28) which converts the signals supplied by the active electrode to binary signals.

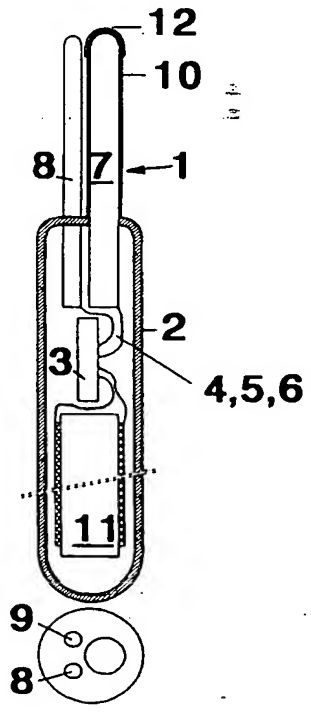

FIG.1

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This invention relates to an implantable biomedical sensor device for measuring in vivo the presence and/or concentration of physiological substances, in particular the concentration of glucose, in the human or animal body.

The traditional glucose sensors are based on the oxidation of glucose by oxygen in the presence of the redox enzyme glucose oxidase (GOd). The flavin adenine dinucleotide (FAD) centre of glucose oxidase is reduced to FADH by glucose (reaction 1). The regeneration of the enzyme occurs through reduction of oxygen to hydrogen peroxide (reaction 2).

GOd-FAD + glucose --> GOd-FADH2 + gluconate (1)

GOd-FADH2 + 02 --> GOd-FAD + H2O2 (2)

The enzyme glucose oxidase is immobilized in gels or membranes which cover an electrode. The glucose content is determined indirectly in one of the following ways:

1. Detection of the decrease in oxygen with a Clark oxygen electrode. A great disadvantage of this method is the sensitivity to the oxygen pressure of the environment.
2. Detection of the hydrogen peroxide production with a hydrogen peroxide electrode.

A drawback of this technique is that hydrogen peroxide degrades the redox enzyme. Another drawback is the high voltage that must be applied, rendering the sensor sensitive to other electroactive components (for instance ascorbic acid) present in biological fluids. Often, biological fluids also contain the enzyme catalase, which breaks down hydrogen peroxide.

In a second generation of glucose sensors, mediators (ferrocene and derivatives) are utilized, which provide for the electron transfer between the redox enzyme and the electrode. The advantage of the use of mediators is that the measurement can be performed at a relatively low voltage, e.g. 350 mV, instead of 800 mV. As a result, by-reactions contribute to a lesser extent to the total current measured. The regeneration of the reduced flavin in glucose oxidase occurs through reduction of the mediator (reaction 3). The reduced mediator is subsequently oxidized electrochemically (reaction 4).

GOd-FADH2 + 2 MedOx --> GOd-FAD + 2 MedRed + 2 H+ (3)

2 MedRed --> 2 MedOx + 2 electrons (at the anode) (4)

Sensors which are based on this principle have the disadvantage that the mediator disappears from the system. Moreover, usable mediators are often toxic, rendering in vivo measurement impossible. Recently, TNO (Dutch Organization for Applied Scientific Research) and the Catholic University of Nijmegen have developed a third generation of glucose sensors, involving direct electron transfer between the redox enzyme and an electrode via a conductive polymer. The basis of the sensor is a filtration membrane having cylindrical pores (Cyclopore, pore diameter 600 nm). By a specially developed polymerization process, the pores of the membrane are coated with polypyrrole, so that hollow fibres of conductive polymer extend perpendicularly through the membrane and are in contact with the measuring fluid. The glucose oxidase is immobilized in the fibres, permitting direct electron transfer between the redox enzyme and the polymer. The location of the enzyme in the pores further provides protection of the enzyme against any influences of the environment, so that it can retain its active structure. After the enzyme has oxidized a glucose molecule (reaction 1), the reduced enzyme can be re-oxidized by transferring electrons to the conductive polymer.

In vitro experiments have shown that glucose concentrations can be measured continuously and accurately for a long time without any loss of sensitivity with a sensor based on a membrane with hollow fibres in which the redox enzyme is located and whose walls are coated with a polypyrrole, this membrane being further provided, on one side thereof, with a platinum film that serves as an electrode. Such a glucose sensor is independent of the oxygen concentration and insensitive to substances such as fructose, citrate, lactate, pyruvate, urea and urea acid.

The object of the present invention is to provide an implantable, contactless, readable glucose sensor device which utilizes a sensor of the third generation as described above. To that end, according to the invention, an implantable biomedical sensor device of the type described above is characterized by a miniaturized electronic responder, which, in an electromagnetic interrogation field, is capable of contactlessly exchanging binary coded information with a transmitter/receiver, this responder being arranged in a closed housing of biocompatible material; and by at least two, but preferably three, electrical connections, passed through the wall of the housing, which constitute electrodes outside the housing, these electrodes comprising at least a work electrode and a counter-electrode, the work electrode comprising a membrane with hollow fibres which extend transversely to the surface of the membrane and whose internal walls are coated with a conductive polymer and in which a redox enzyme is located and which, at one

end thereof, are in contact with the associated electrical connection, this electrical connection being coupled to a processing device which receives the signals supplied by the work electrode in operation and converts these signals into binary signals. In order to provide a constant voltage between the fluid and the work electrode, it is preferred that a third electrode is arranged, for instance an Ag/AgCl reference electrode.

It is noted that implantable electronic responders per se are already known. Dutch patent application 8701541, for instance, discloses the use of an implantable responder for the identification of livestock. Also, implantable responders are already utilized in practice for the identification of cattle and pigs. The known implantable responders are arranged in a glass tube melted up at its ends and comprise a resonant circuit whose coil at least partly constitutes the antenna for receiving an electromagnetic interrogation field generated by a transmitter or a transmitter/receiver. The interrogation field can bring the resonant circuit into resonance and the alternating voltage generated across the resonant circuit is used, after being rectified, as supply voltage for the digital circuits of the responder. The digital circuits comprise a code signal generator and can further comprise a clock pulse shaper. However, the clock pulses can also be derived directly from the tops of the alternating voltage across the resonant circuit. After receiving supply voltage and clock pulses, the code signal generator generates a binary code signal, which is used to control a switching means, for instance a transistor. The switching means is connected to the resonant circuit and can modulate the resonant frequency and/or the damping of the resonant circuit in the rhythm of the binary code signal. This modulation can be detected by a transmitter/receiver or by a separate receiver. These techniques are known per se. One example of a suitable responder is disclosed in U.S. Patent 4,196,418, which is considered to be incorporated herein as a reference.

It is further noted that a biomedical sensor device according to the invention can naturally be used for measurement in vitro as well.

Hereinafter, the invention will be further described, by way of example only, with reference to the accompanying drawings of one exemplary embodiment.

Fig. 1 schematically shows on an enlarged scale an example of an implantable sensor device according to the invention in side view and in top plan view;

Fig. 2 schematically shows on a yet further enlarged scale a part of the sensor device of Fig. 1;

Fig. 3 shows an example of an electrical block diagram of a sensor device according to the invention; and

Fig. 4 shows a modification of the device of Fig. 1.

Figure 1 schematically shows an example of an implantable sensor device 1 according to the invention. The sensor device comprises a capsule 2, which, in the embodiment shown, consists of a glass tube which has been melted up at both ends. However, any other biocompatible and permanently fluid-tight material is usable. It is also possible to use a different shape than a tubular shape. A tubular shape, however, permits ready implantation by means of a hollow needle.

Disposed in the capsule is the electronic circuit 3 of the responder. The electronic circuit is connected to the electrodes located outside the capsule by means of a plurality of electrical connections. In the embodiment shown, three connections 4, 5 and 6 with associated electrodes 7, 8 and 9 are used. In the embodiment shown, the electrodes 7, 8 and 9 project from the end of the capsule.

Electrode 8 is the counter-electrode, which may be made of a suitable noble metal, such as for instance platinum, or may be coated with such a metal. Electrode 9 is an Ag/AgCl reference electrode providing for a constant voltage between the work electrode and the fluid.

The work electrode 10 is a composite electrode, comprising a membrane with cylindrical pores. A suitable membrane is for instance the membrane available under the name of Cyclopore. The pore diameter may for instance be 600 nm. The pores constitute hollow fibres extending transversely to the surfaces of the membrane.

To protect the tip of the work electrode, a cap 12 may be arranged, which is made of a biocompatible plastics material suitable for the purpose.

The surface of the work electrode is shown in more detail in Fig. 2. The walls of the hollow fibres 14 are coated with an electrically conductive polymer layer 15, for instance made of polypyrrole. In the pores, the redox enzyme glucose oxidase is immobilized, as indicated at 16, so that direct electron transfer between the redox enzyme and the polymer layer is possible. In the pores, the enzyme is protected against ambient influences, yet communicates with the body fluids 17 present around the sensor device.

It is noted that it is already known from the literature that there is a clear relationship between the glucose concentration in the blood stream and the glucose concentration in the tissue. Accordingly, measurement of the glucose concentration with the aid of a sensor device implanted in the tissue is equivalent to direct measurement in the blood stream. On one side of the membrane, the

hollow fibres of the membrane 13 are connected to the core 7 of the work electrode. For that purpose, a conductive layer 18 is provided on that side of the membrane. The conductive layer 18 may for instance consist of a thin layer of platinum of a suitable thickness. The thickness of the platinum layer is not critical and may for instance be between 50 and 400 nm. The platinum film is in direct or indirect electrical contact with the core 7 of the work electrode, which has been passed through the wall of the capsule 2 so as to be sealed relative thereto. The platinum layer can for instance be applied to the membrane by sputtering.

In order to improve the biocompatibility of the sensor device, the side of the membrane that comes into contact with the body fluids can be provided with a film 19 of a suitable metal or a suitable plastics, such as for instance high-density poly-lactic acids. If a metal film is applied, this may for instance be a platinum film, applied through sputtering. It has been found that if the sputtered layer has a thickness of 100 nm, the membrane is still sufficiently porous to allow the desired interaction between the glucose and the redox enzyme. It is also possible to use, for instance, titanium, instead of platinum. An advantage of a metal covering layer is that it can be connected to the counter-electrode 8 at the same time so as to realize the desired potential difference across the membrane.

A potential difference of 0.35 volts provides good results. If the contact surface between the membrane and the fluid has an area of no more than 15 mm2 and the potential difference is 0.35 volts, currents of the order of 100-1,000 nA are measured. This means that the contact surface and/or the potential difference can be reduced still further. It has been found that the operation of a sensor device as described above is independent of the oxygen concentration as well as the presence of fructose, citrate, lactate, pyruvate, glutathione, urea and urea acid in mM concentrations. Ascorbic acid, however, is capable of influencing the measuring result. This problem can be solved by measuring at a lower potential difference of, for instance, about 0.20 volts and/or by the use of a permselective second membrane, covering the electrode 10 with the membrane 19. This second membrane is impermeable to the charged ascorbic acid, but permeable to the neutral glucose molecule and the oxidation product of glucose (gluconolactone).

If so desired, the permselective membrane can be alternatively constructed as a cap surrounding all electrodes, which is arranged on the capsule. Such a cap is shown at 30 in Fig. 4. The cap 30 surrounds the electrodes 7, 8 and 9 with some clearance. The body fluid, at any rate certain components thereof, such as glucose, can penetrate into this space between the cap and the electrodes.

Alternatively, it is possible to measure with the aid of two electrodes of which only one contains the redox enzyme. The influence of other electroactive molecules can then be eliminated and the differential signal can then be unequivocally ascribed to the glucose.

Fig. 3 schematically shows a responder circuit 20 for a sensor device according to the invention. The responder circuit comprises an input circuit 21 with a coil 22 which may or may not be tuned with the aid of a capacitor. The coil 22 may be provided with a ferrite core 11 and at the same time constitutes an antenna. The input circuit 21 is connected with a rectifier circuit 24 producing a preferably stabilized supply voltage starting from the voltage induced by an interrogation field in the input circuit in operation. The supply voltage is applied to the various active components of the responder circuit 20. Further, starting from the supply voltage, the measuring voltage to be set across the membrane in operation is formed, for instance by means of a so-called potentiostat 25.

The responder circuit can further comprise a clock pulse generator 26, capable of providing clock pulses for the control of the digital circuits. In principle, it is also possible to use the tops of the alternating voltage induced in the receiver circuit as clock signals. If the responder circuit is provided with an identification code, this code is stored in a memory 27. The memory may be wirelessly programmable. In that case, a demulator, which is not shown in Fig. 3, is connected between the receiver circuit and the memory. Fig. 3 does show an A/D converter 28, which receives the current signals supplied by the work electrode 10 and converts them to the binary signals which can be stored in the memory 27 or a part thereof. In operation, the output signals of the memory are applied to a modulation means 23, which may for instance be a switching means, capable of modulating the electrical properties of the receiver circuit and hence the energy absorption of the receiver circuit.

Instead of the memory and the A/D converter, a microprocessor could be used. The measured signals are preferably represented as binary signals of eight bits or more.

The electrode 10 can in principle be arranged on a curved surface at the ends of the capsule or on a flattened part, but is preferably arranged on a projecting electrode part 7.

Further, the responder circuit described is a passive circuit, which means that the required supply energy is drawn from the interrogation field. It is also possible, however, to arrange a battery in the capsule.

The sensor device can be activated by bringing a transmitter/receiver, preferably of portable

design, into the vicinity of the implanted sensor device to generate an electromagnetic interrogation field having a frequency that is suitable for the sensor device in question. After being activated, the sensor device can measure the glucose concentration in the surrounding tissue by means of the current generated by the membrane electrode 10. The current intensity is converted by the A/D converter to a digital signal, which, alone or together with a binary code, is used to modulate the energy absorption of the receiver circuit. This modulation is detected by the transmitter/receiver and converted to a measured value.

If the sensor device comprises a so-called battery, the measuring signal could alternatively be optionally emitted via a separate antenna coil. This, however, requires a sensor device of greater dimensions, which may be objectionable.

The value of the glucose content as detected by the transmitter/receiver can be used to control an insulin pump, if necessary. If an implanted insulin pump is used, this pump, too, can in principle be wirelessly energized with the same transmitter/receiver or a special transmitter.

For measurement, preferably the chrono-amperometry technique is used. According to this technique, the instantaneous current intensity is measured at a predetermined time after the occurrence of a potential jump. This predetermined time may be prior to the time at which a stable final condition has been reached, that is, if the relation is known between the measured value at the time chosen and the measured value in the stable final condition.

In the case where the glucose concentration in the tissue is measured, after the voltage has been switched on, the current in the work electrode is measured at a time halfway between the time of activation and the time at which the stable condition is reached. This is the so-called half-value time $t_{\frac{1}{2}}$. The half-value time may be fixed in the responder itself by means of a suitable timer circuit, for instance a shift register or a counter, or may be determined in the transmitter/receiver or by the user. This technique enables a faster measuring procedure and, moreover, the redox enzyme is brought in the activated condition only for a short time. It is expected that this technique will contribute to a long life of the sensor device.

It is noted that, after the foregoing, various modifications will readily occur to a person of ordinary skill in the art. Thus, various embodiments of the responder circuit are possible. t is also possible to measure the presence and/or concentration of other substances, for instance lactose, in the human or animal body or in vitro, in the manner described, with the aid of a suitable enzyme. Sucb modifications are understood to fall within the scope of the present invention.

Claims

1. An implantable biomedical sensor device for measuring in vivo the presence and/or concentration of physiological substances, in particular the concentration of glucose, in the human or animal body, characterized by a miniaturized electronic responder, which, in an electromagnetic interrogation field, is capable of contactlessly exchanging binary coded information with a transmitter/receiver, this responder being arranged in a closed housing of biocompatible material; and by at least two electrical connections, passed through the wall of the housing, which constitute electrodes outside the housing, these electrodes comprising at least a work electrode and a counter-electrode, the work electrode comprising a membrane with hollow fibres which extend transversely to the surface of the membrane and whose internal walls are coated with a conductive polymer and in which a redox enzyme is disposed and which, at one end thereof, are in contact with the associated electrical connection, this electrical connection being coupled to a processing device which receives the signals supplied by the work electrode in operation and converts these signals to binary signals.

2. An implantable sensor device according to claim 1, characterized by a reference electrode which has been passed through the wall of the housing.

3. An implantable sensor device according to claim 1, characterized in that the membrane, on one side thereof, is provided with a thin conductive layer, which is electrically connected with the associated electrical connection.

4. An implantable sensor device according to claim 1, 2 or 3, characterized in that the membrane is arranged on a projecting electrode core.

5. An implantable sensor device according to claim 1, 2 or 3, characterized in that the membrane, with interposition of a thin conductive layer, is arranged directly on a part of the outer wall of the closed housing of the responder.

6. An implantable sensor device according to claim 3, 4 or 5, characterized in that the thin conductive layer is a metal layer.

7. An implantable sensor device according to claim 6, characterized in that the metal layer is a platinum layer.

8. An implantable sensor device according to claim 6 or 7, characterized in that the metal layer is applied by sputtering.

9. An implantable sensor device according to any one of the preceding claims, characterized in that the free surface of the membrane is coated with a thin layer of biocompatible material.

10. An implantable sensor device according to claim 9, characterized in that the biocompatible material is a synthetic material.

11. An implantable sensor device according to claim 9, characterized in that the biocompatible material is a metal layer applied by sputtering.

12. An implantable sensor device according to claim 11, characterized in that the metal layer is connected as counter-electrode.

13. An implantable sensor device according to any one of the preceding claims 2-12, characterized in that the reference electrode is an Ag/AgCl electrode.

14. An implantable sensor device according to any one of the preceding claims 2-12, characterized in that the reference electrode is provided with a permselective biocompatible membrane.

15. An implantable sensor device according to any one of the preceding claims, characterized in that the membrane is covered with a permselective second membrane.

16. An implantable sensor device according to claim 15, characterized in that the second membrane is designed as a cap arranged over the electrodes and connecting to the housing.

17. An implantable sensor device according to any one of the preceding claims, characterized by a second work electrode comprising a membrane with hollow fibres whose internal wall is coated with a conductive polymer, whilst in the hollow fibres of the second membrane no redox enzyme is disposed and the processing device comprises a device that shapes the difference of the signals supplied by the two work electrodes.

18. An implantable sensor device according to any one of the preceding claims, characterized in that the conductive polymer is polypyrrole.

19. An implantable sensor device according to any one of the preceding claims, characterized in that the responder is designed for generating in operation a stable voltage of about 0.35 volts or less across the membrane.

20. An implantable sensor device according to any one of the preceding claims, characterized in that the responder comprises a timer circuit which effects the measurement of the signal supplied by the work electrode at a predetermined time after activation of the responder.

21. An implantable sensor device according to any one of the preceding claims, characterized in that the responder is a passive responder.

22. An implantable sensor device according to any one of the preceding claims, characterized in that the responder in operation draws electrical energy from a built-in battery.

23. An implantable sensor device according to any one of the preceding claims, characterized in that the housing of the responder has a flattened part, on which a membrane of a work electrode is arranged.

24. An implantable sensor device according to any one of the preceding claims, characterized in that the responder comprises a potentiostat, which, in operation, generates a stable voltage between the reference electrode and the work electrode.

25. A system comprising one or more implantable biomedical sensor devices according to any one of claims 1-24 and at least one transmitter/receiver capable of generating an electromagnetic interrogation field for activating an implanted sensor device and reading out said device.

26. A system according to claim 24, characterized by an electrically controllable insulin pump.

27. A system according to claim 25, characterized in that the transmitter/receiver is designed to control the insulin pump.

28. A system comprising a contactless sensor device for measuring the presence and/or concentration of physiological substances, in particular the concentration of glucose, according to any one of the preceding claims, characterized in that the sensor is not implanted, but is

used in vitro for assaying the presence and/or concentration of physiological substances in a process or reaction vat.

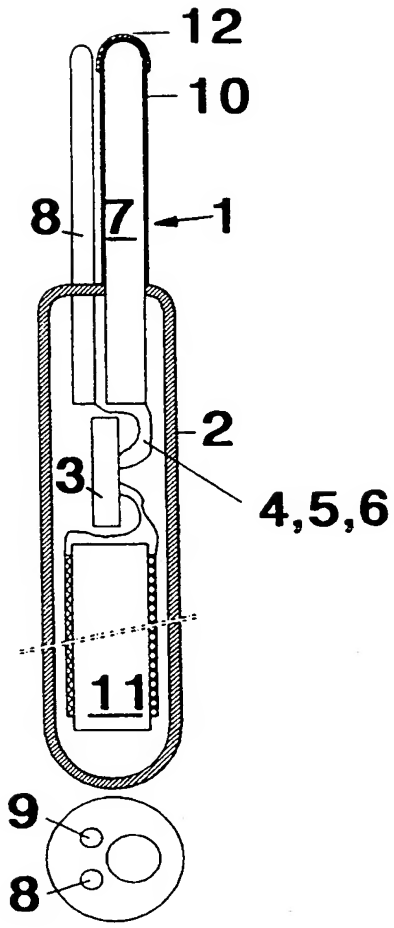

FIG.1

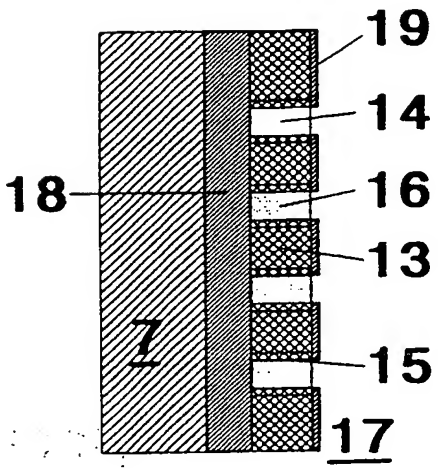

FIG. 2

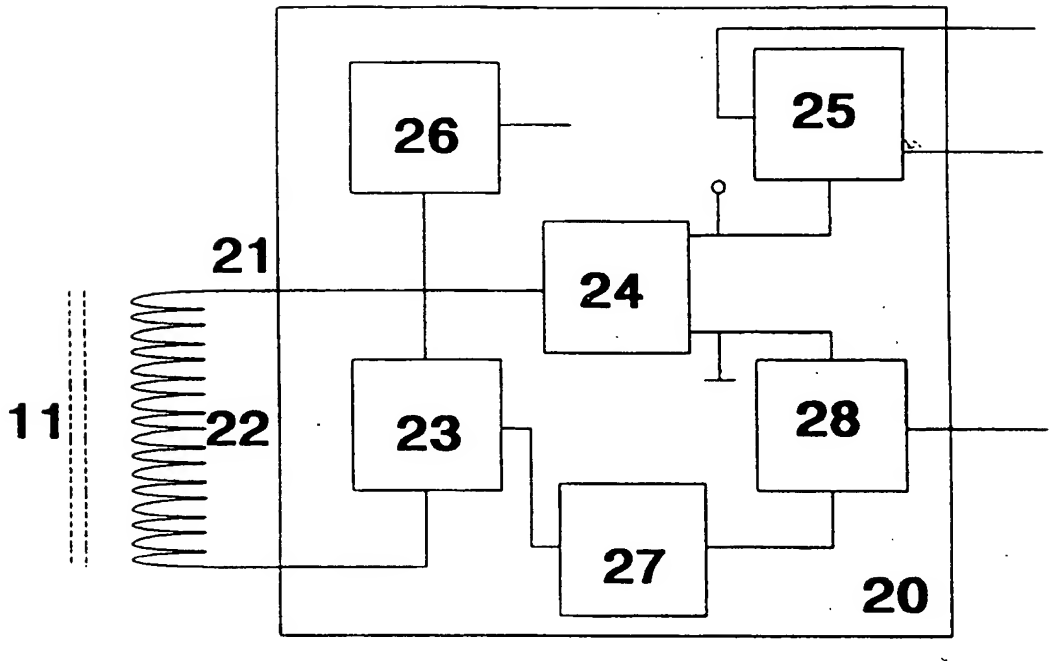

FIG. 3

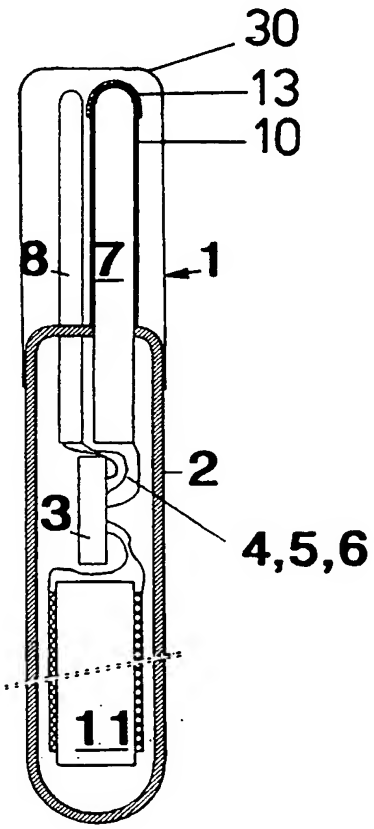

FIG. 4

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 20 0278

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X Y A A	WO-A-9 104 704 (F. NEFTEL) * page 4, line 7 - line 24; figures 1,2 * * page 5, line 22 - line 34 * * page 6, line 1 - line 38 * * page 9, line 17 - line 22 *	25-27 1 9,10,15 17,21,23	A61B5/00 C12Q1/00
Y A	US-A-4 655 880 (CHUNG-CHIUN LIU) * column 6, line 12 - column 11, line 65 *	1 2,13,22, 24,26,25	
A	HEPATO-GASTROENTEROLOGY vol. 31, no. 6, December 1984, STUTTGART (DE) pages 285 - 288 M. KESSLER ET AL. 'A New Glucose Electrode for Tissue Measurements' * page 286; figure 2 *	1-3,5,6, 12-15, 22,23	
A A	EP-A-0 245 073 (UNIVERSITY OF CALIFORNIA) * page 9, line 14 - page 18, line 9; figures 2,5,6 *	1,4,13 17,22, 24,25	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A A	EP-A-0 453 283 (TEKNEKRON) * column 2, line 18 - column 3, line 34 *	3,6-8,13 28	A61B

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	28 APRIL 1993	RIEB K.D.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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E : earlier patent document, but published on, or after the filing date
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